Diuretic-Induced Hypokalemia in Uncomplicated Systemic Hypertension: Effect of Plasma Potassium Correction on Cardiac Arrhythmias

VASILIOS PAPADEMETRIOU, MD, ROSS FLETCHER, MD, IMBRAHIM M. KHATRI, MD and EDWARD D. FREIS, MD

Sixteen patients with diuretic-induced hypokalemia underwent 24-hour ambulatory electrocardiographic monitoring during and after correction of hypokalemia. Plasma potassium averaged 2.83 ± 0.08 mEq/liter before and 3.73 ± 0.06 mEq/liter after correction with potassium chloride, triamterene or both. Premature atrial contractions decreased in 6 patients, increased in 6 and remained unchanged in 4. There was no improvement in ventricular ectopic activity after plasma potassium correction. Ventricular ectopic activity improved in 5 patients, worsened in 10 and remained unchanged in 1. Ventricular tachycardia was not observed in either phase. Plasma magnesium remained normal throughout. The investigators conclude that in patients with uncomplicated hypertension, correction of diuretic-induced hypokalemia does not significantly reduce the occurrence of spontaneous atrial or ventricular ectopic activity.

(Am J Cardiol 1983;52:1017-1022)

Of all patients who receive a thiazide diuretic for the treatment of essential hypertension, in 20 to 40% hypokalemia will develop.[1,2] Because of side effects associated with hypokalemia, potassium chloride or potassium-sparing diuretics are often administered to patients who receive diuretic therapy. Considering the number of patients who receive diuretic therapy, it is not surprising that the amount of potassium chloride prescribed annually is estimated to be 20 to 30 billion milliequivalents.[3] This practice has been maintained despite several recent reports that question the need for routine potassium replacement therapy and even point out the potential risk of such treatment.[3-5]

An increase in cardiac arrhythmias is considered one of the major risks associated with hypokalemia. The increased susceptibility to digitalis-related arrhythmias in hypokalemic patients has been well documented[6,7] and is widely accepted. However, in patients with hypertension uncomplicated by cardiac disease, an association between thiazide-induced hypokalemia and an increased incidence of arrhythmias has not been established, and the subject remains controversial. Examining routine electrocardiograms retrospectively, Pick[8] concluded that a potassium deficit by itself can only exceptionally affect the formation and conduction of normal impulses, whereas Davidson et al[9] suggested that patients with hypokalemia without heart disease who do not take digitalis had an increased incidence of ectopic beats. However, examination of routine electrocardiograms is a poor indicator of cardiac ectopic activity, and conclusions drawn from these studies cannot be considered representative or reliable.

The present study investigates prospectively the effect of correction of hypokalemia on cardiac arrhythmias in patients with uncomplicated hypertension and hypokalemia secondary to long-term diuretic therapy. Twenty-four-hour ambulatory electrocardiographic recording was selected as the most reliable method of identifying cardiac arrhythmias.[10,11]

Methods

Patients: Twenty-one hypertensive patients entered the study; all of them had a serum potassium level ≤3.2 mEq/liter while receiving diuretic treatment. Patients were excluded from the study if they had a history of myocardial infarction, angina pectoris, congestive heart failure, renal insufficiency (creatine ≥2.0 mg/dl), active peptic ulcer, significant mental

From the Veterans Administration Medical Center, Washington, DC. Manuscript received April 12, 1983; revised manuscript received July 8, 1983, accepted July 12, 1983.

Address for reprints: Vasilios Papademetriou, MD, Veterans Administration Medical Center (151E), 50 Irving Street, NW, Washington, DC 20422.

TABLE I Patient Characteristics

Pt	Race	Age (yr)	Anti-HTN Medication*	Hypokalemic Phase		Normokalemic Phase		Daily Dose of	
				PK	PMg	PK	PMg	KCl (mEq)	Triam (mg)
1	B	57	P, M, HCTZ	2.9	1.6	3.5	1.6		150
2	B	59	M, HY, HCTZ	2.2	1.5	3.5	1.7	72	200
3	B	69	HCTZ	3.2	1.3	3.9	1.4	72	
4	B	54	M, HCTZ	2.8	1.4	3.8	1.4	96	
5	B	55	P, HCTZ	2.9	1.5	3.5	1.6		200
6	W	29	P, CH	2.9	1.9	3.5	1.7	72	
7	W	61	CL, HY, HCTZ	2.9	2.0	4.1	1.6	72	
8	B	59	R, CH	2.9	1.4	3.8	1.7	48	200
9	B	56	HCTZ	2.5	1.3	3.8	1.4	48	200
10	B	52	P, CH	3.2	1.6	3.9	1.4	48	
11	B	44	HCTZ	3.2	1.2	3.7	1.7		200
12	B	59	HCTZ	2.7	1.2	3.6	2.0		100
13	B	45	HCTZ	3.0	1.6	3.7	1.8	96	
14	B	45	CL, CH	2.6	—	3.6	—	96	
15	B	48	HCTZ	2.3	—	4.3	—	48	200
16	B	52	HCTZ	3.0	1.3	3.5	1.2	48	
Mean ± SEM		52.75 ± 2.3		2.83 ± 0.08	1.49 ± 0.06	3.73 ± 0.06	1.59 ± 0.06		

CH = chlorthalidone; CL = clonidine; HCTZ = hydrochlorothiazide; HTN = hypertension; HY = hydralazine; KCl = potassium chloride; M = methyldopa; P = propranolol; PK = plasma potassium; PMg = plasma magnesium; R = reserpine; Triam = triamterene.

illness, digitalis therapy for any reason or peripheral edema of any origin. Five patients were terminated from the trial: 3 because of noncompliance, 1 patient because he developed depression while receiving reserpine and chlorthalidone and left the study and 1 because he developed overt hyperglycemia that required insulin treatment. Of the 16 patients who completed the study, 14 were black and 2 were white. They were 29 to 69 years old (mean ± standard error of the mean [SEM] 53 ± 2). Twelve of the 16 patients had normal electrocardiograms, 2 had left ventricular hypertrophy by voltage criteria only and 2 had nonspecific changes in leads III and aVF. All patients had been receiving treatment for essential hypertension that included diuretic therapy for 4 to 48 months (mean 17 ± 3) before entering the study. Twelve patients were taking hydrochlorothiazide, 50 mg twice daily, and 4 were taking chlorthalidone, 50 mg once daily. Hypertension was controlled with hydrochlorothiazide alone in 7 patients and 9 required regimens of 2 or 3 drugs that included methyldopa, propranolol, clonidine, reserpine or hydralazine in addition to the diuretic (Table I). The antihypertensive regimen did not change throughout the study. All patients required potassium chloride supplement or a potassium-sparing diuretic to maintain near-normal serum potassium levels before the study.

No specific dietary instructions were given other than to observe moderate salt restriction; that is, to avoid heavily salted foods and to add no salt at the table.

Study protocol: All patients were seen every 2 weeks. At each visit throughout the study, sitting blood pressure, heart rate, body weight and plasma creatine, sodium, potassium, chloride and magnesium concentrations were determined. Blood samples were collected in sterilized 10-ml tubes that contained 143 units of lithium heparin and were analyzed within 30 minutes.

Phase 1—Screening phase: Potassium chloride or potassium-sparing diuretic therapy was discontinued and patients were seen every 2 weeks. Antihypertensive therapy was continued. Only patients whose plasma potassium level was reduced to ≤3.2 mEq/liter during any 1 of a possible 4 successive visits were included in the study. Once hypokalemia was confirmed by this criterion (plasma potassium ≤3.2 mEq/liter), additional tests, including 12-lead electrocardiography and arterial blood pH and gas determinations were performed. Twenty-four-hour ambulatory electrocardiographic monitoring was initiated within 2 hours after hypokalemia was confirmed and completed before replacement therapy with potassium chloride was begun.

Phase 2—Potassium chloride replacement therapy: After baseline studies described under phase 1 in all patients with plasma potassium ≤3.2 mEq/liter, replacement therapy was initiated with 3 tablets of 8 mEq of potassium chloride in a wax matrix ("Slow-K") 2 times daily (48 mEq/day). The dose of potassium chloride was increased every 2 weeks until hypokalemia was successfully corrected or the maximum dose of 96 mEq/day was given. Successful correction of hypokalemia was considered to have been achieved when the plasma potassium was ≥3.5 mEq/liter and was at least 0.5 mEq/liter higher than the unsupplemented baseline value. In patients who achieved correction of hypokalemia, 24-hour ambulatory electrocardiographic monitoring, 12-lead electrocardiography and arterial blood gases and pH were obtained on the same visit that the correction of plasma potassium became manifest.

Phase 3—Triamterene alone or with potassium chloride: All patients who completed phase 2 entered phase 3. Potassium chloride therapy was discontinued and hypokalemia (plasma potassium ≤3.2 mEq/liter) was allowed to recur after which triamterene, 50 mg twice daily, was begun. The dose of triamterene was increased every 2 weeks until hypokalemia was successfully corrected or the maximum dose of 200 mg/day had been given. In patients whose hypokalemia had not been corrected with the maximum dose of either potassium chloride or triamterene, a combination therapy of triamterene and potassium chloride was instituted. Again on the same visit that plasma potassium was found normalized, 24-hour ambulatory electrocardiographic monitoring and 12-lead electrocardiography were performed and arterial blood gas was obtained from patients whose hypokalemia was not corrected in phase 2 but was corrected in phase 3. Arterial blood samples were taken before and after correction of hypokalemia from 12 patients. The 4 other patients refused sampling.

Ambulatory electrocardiographic monitoring: Ambulatory electrocardiographic monitoring was carried out for 24 hours using a double-channel model 425 Avionics recorder, and analysis was performed on a model 660A Avionics 2 channel electrocardioscanner. Analysis of all tapes was carried out by an experienced technician. For quality control, 80% of the tapes were also analyzed by a second technician. Minimal

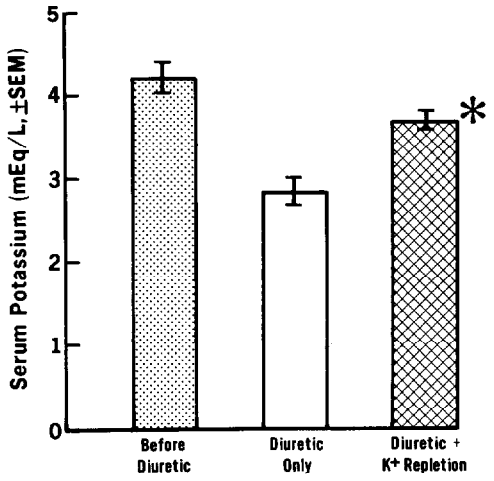

FIGURE 1. Plasma potassium (K^+) levels before any diuretic therapy, on diuretic therapy alone and after correction with potassium chloride triamterene or both. *p <0.0001. SEM = standard error of the mean.

interobserver variability was found. In addition, samples from each hour of recording, including the important arrhythmias, were printed on hard copies, in real time, and were reviewed by 1 of the investigators.

Cardiac arrhythmias were tabulated for convenience under subgroups as follows: (1) supraventricular—premature atrial contractions (PACs) 1 to 9, 10 to 49 or ≥50 per hour. Supraventricular tachycardia, atrial flutter or fibrillation and atrioventricular disturbances were reported as separate events. (2) Ventricular arrhythmias—premature ventricular contractions (PVCs) unifocal 1 to 9, ≥10 per hour, multifocal 1 to 9, ≥10/hour, PVCs in couplets and ventricular tachycardia.

Statistical analysis of the results was performed where appropriate using Student's *t* test for paired observations. Fisher's exact probability test was used to determine statistical significance between patients with couplets before and after correction of hypokalemia.[12]

Results

The 16 patients who constituted the study group were known to have had hypokalemia in the past and had been receiving potassium chloride or a potassium-sparing diuretic. Review of the charts of 14 of these patients for which pretreatment data could be found revealed that they had normal serum potassium levels (4.20 ± 0.09, mean ± SEM) before diuretic therapy for hypertension. In all except 1 patient, the plasma potassium was reduced to ≤3.2 mEq/liter within the first 2 weeks after the potassium chloride or the potassium-sparing diuretic was discontinued. In the 14 patients with prediuretic serum potassium of 4.20 ± 0.09 mEq/liter, the unsupplemented plasma potassium was reduced to 2.83 ± 0.08 mEq/liter (range 2.20 to 3.20) (Fig. 1).

After correcting hypokalemia with either potassium chloride alone, triamterene alone or a combination, the plasma potassium was increased to 3.73 ± 0.06 mEq/liter (range 3.50 to 4.30) (p <0.0001). Of the 16 patients, only 8 were corrected with potassium chloride alone in doses up to 96 mEq/day. Of the remaining 8, 4 were corrected with triamterene alone in doses up to 200 mg/day and 4 required the combination of triamterene 200 mg plus potassium chloride in doses of 48 to 72 mEq/day.

TABLE II Changes in Acid Base Balance (n = 12)

	During Hypokalemia	After K Repletion	p Value
Arterial blood pH	7.43 ± 0.01	7.41 ± 0.01	NS
Arterial $PaCO_2$	43 ± 2	40 ± 1	NS
Arterial HCO_3	28 ± 1	24 ± 1	0.02
Urine pH	6.42 ± 0.34	5.83 ± 0.21	NS

K = potassium; NS = not significant.

The mean plasma magnesium was 1.49 ± 0.06 mEq/liter during the hypokalemic phase and 1.59 ± 0.06 mEq/liter after potassium repletion (Table I). This difference was not statistically significant. Although several patients had low borderline plasma magnesium levels of 1.2 or 1.3 mEq/liter (normal range 1.3 to 2.1), there was no correlation between plasma magnesium levels and the occurrence of cardiac arrhythmias.

The mean arterial blood pH, CO_2, HCO_3 and urinary pH were examined in 12 patients before and after correction of hypokalemia (Table II). Although the mean values were within normal limits, values for individual patients indicated mild metabolic alkalosis during the hypokalemic phase. Although no significant change occurred in pH or $PaCO_2$ after correction of hypokalemia, a significant (p <0.02) reduction in HCO_3 concentration was observed, indicating a shift to a less alkaline state. No change was observed in the acidity of the urine. However, these changes in the acid-base balance between the 2 phases were mild and it is very unlikely that they significantly affected the ratio of intracellular to extracellular potassium.

Table III shows the occurrence of cardiac arrhythmias during hypokalemia and after potassium repletion in all 16 patients individually. With respect to supraventricular arrhythmias, 9 patients were free of PACs for the total 24-hour monitoring during the hypokalemic phase, compared with 7 patients after potassium repletion. The number of PACs decreased in 6 patients after hypokalemia was corrected. However, in 6 other patients the occurrence of PACs increased. In the remaining 4 there was no change. In addition to PACs during the hypokalemic phase, 3 patients had supraventricular tachycardia for 2 to 14 seconds. After potassium repletion 1 patient had supraventricular tachycardia for 4 seconds. One patient had atrioventricular dissociation with junctional rhythm during both phases, which occurred during sleep in both monitorings and was associated with a slow atrial rate.

Ventricular ectopic activity decreased in 5 patients after potassium repletion. However, in 10 patients, ventricular ectopic activity increased after potassium repletion as compared with that in the hypokalemic phase. Patient 6 showed no change between the 2 phases. Comparing ventricular arrhythmias that occurred during the hypokalemic phase with those after

TABLE III Changes in Cardiac Arrhythmias Before and After Correction of Hypokalemia (Number of Hours Per 24-Hour Monitoring)

		Supraventricular Arrhythmias						Ventricular Arrhythmias						
		PACs							Unifocal PVCs		Multifocal PVCs			
Pt	PK	0	1–9/h	10–49/h	≥50/h	SVT (s)	A-VD (h)	0	1–9/h	≥10/h	1–9/h	≥10/h	Couplets	VT
1	2.9	24	...	...	...	...	...	21	3	...	...	...	...	...
	3.5	15	6	...	...	...	...	10	11	...	...	...	1	...
2	2.2	17	7	...	...	...	...	13	10	...	1	...	...	...
	3.5	24	...	...	...	...	...	2	20	...	...	2	2	...
3	3.2	1	...	...	23	14	...	...	...	...	5	18	4	...
	3.9	1	...	8	15	...	...	...	7	1	7	9	2	...
4	2.8	23	1	...	...	2	...	14	10	...	...	...	...	...
	3.8	11	13	...	...	...	...	24	...	...	...	...	...	...
5	2.9	24	...	...	...	...	...	24	...	...	...	...	...	...
	3.5	21	3	...	...	...	...	19	4	...	1	...	...	...
6	2.9	24	...	...	...	...	...	23	1	...	...	...	...	...
	3.5	24	...	...	...	...	...	23	1	...	...	...	...	...
7	2.9	21	...	...	...	...	...	19	2	...	...	...	...	...
	4.1	...	15	1	5	4	...	15	1	...	5	...	1	...
8	2.9	21	2	1	...	10	...	24	...	...	...	...	...	...
	3.8	24	...	...	...	...	...	22	2	...	...	...	...	...
9	2.5	1	13	8	...	...	...	13	7	...	2	...	...	...
	3.8	20	4	...	...	...	...	2	...	...	...	21	3	...
10	3.2		6	12	5	...	...	10	7	1	2	3	...	...
	3.9		17	5	...	...	...	12	2	5	4	...	...	...
11	3.2	24	...	...	...	...	...	20	5	...	...	...	...	...
	3.7	24	...	...	...	...	...	22	2	...	3	...	...	...
12	2.7	24	...	...	...	...	...	20	3	...	...	...	...	...
	3.6	24	...	...	...	...	...	24	...	...	...	...	...	...
13	3.0	20	3	...	...	...	...	21	2	...	...	...	...	...
	3.7	24	...	...	...	...	...	21	3	...	...	...	...	...
14	2.6	24	...	...	...	...	...	22	2	...	...	...	...	...
	3.6	23	1	...	...	...	...	19	3	...	1	...	1	...
15	2.3	24	...	...	...	...	...	12	9	...	2	...	...	...
	4.3	24	...	...	...	...	...	23	1	...	...	...	...	...
16	3.0	24	...	...	...	...	8	21	2	...	1	...	...	...
	3.5	19	5	...	...	...	8	9	9	...	5	...	...	...

A-VD = atrioventricular dissociation; PAC = premature atrial contractions; PK = plasma potassium; PVC = premature ventricular contractions; SVT = supraventricular tachycardia; VT = ventricular tachycardia.

potassium repletion, there was no improvement in the group as a whole. In fact, the mean number of hours per monitoring during which each group of arrhythmias was observed was slightly greater after potassium repletion in all groups of ventricular arrhythmias than it was before (Table IV).

Figure 2 shows the distribution of patients according to the most severe or complex types of arrhythmias. There was a trend toward more complex types of arrhythmias after potassium repletion. For example, although only 1 patient had couplets during the hypokalemic phase, 6 patients had couplets after potassium repletion. However, this change was not statistically significant.

Discussion

The major objective of this study was to determine whether correction of hypokalemia in patients with otherwise uncomplicated hypertension results in a decrease of cardiac arrhythmias. Only patients with overt hypokalemia (plasma potassium ≤3.2 mEq/liter) were selected. Long-term diuretic treatment was considered essential for the purpose of the study, and no attempt was made to discontinue diuretic treatment at any time.

The results provided no evidence that correction of hypokalemia would reduce the incidence of cardiac arrhythmias. These results are in contrast to those recently reported by Holland et al.[13] The 2 studies were similar in that both dealt with patients with uncomplicated hypertension with diuretic-induced hypokalemia who were of similar age (29 to 64 years in Holland's study and 29 to 68 years in ours). However, several differences in the design of the studies may account for the different outcomes. In Holland's study, diuretic treatment was discontinued and the serum potassium levels were allowed to increase to normal. Patients with more than minimal ventricular ectopic activity during the prediuretic phase were excluded. By selecting only patients without significant arrhythmias during the normokalemic phase, there was little or no possibility of improvement of ventricular ectopic activity by chance when hypokalemia was present. Several investigators have shown considerable day-to-day spontaneous variability of ventricular arrhythmias detected by long-term electrocardiographic recording.[14,15] Thus, the association of the arrhythmias observed during the diuretic phase with low plasma potassium is not justified.

Of the 21 patients who entered their study, 7 developed complex ventricular ectopic activity during

TABLE IV Number of Hours Per 24-Hour Monitoring that Each Group of Arrhythmias Was Observed

VEA	Hypokalemic Phase	K Repletion Phase
0	17.31 ± 1.62	14.06 ± 2.05
Unifocal PVCs; 1–9/h	3.75 ± 0.87	4.50 ± 1.33
Unifocal PVCs; ≥10/h	0.13 ± 0.09	0.50 ± 0.33
Multifocal PVCs; 1–9/h	1.19 ± 0.44	1.75 ± 0.58
Multifocal PVCs; ≥10/h	1.38 ± 1.13	2.00 ± 1.39
Couplets	0.25 ± 0.25	0.63 ± 0.24
VT	0	0

Values are mean ± standard error of the mean.
K = potassium; PVC = premature ventricular contractions; VEA = ventricular ectopic activity; VT = ventricular tachycardia.

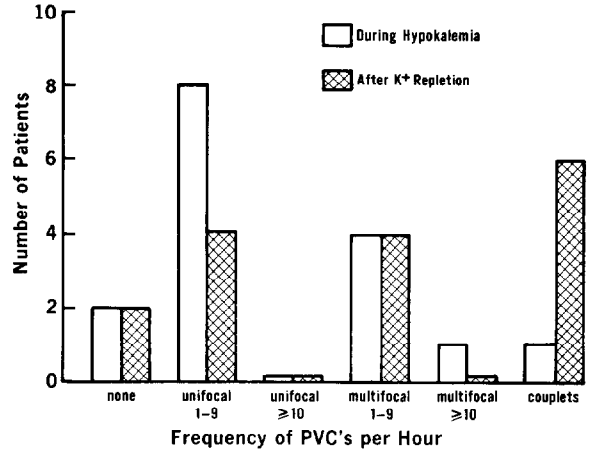

FIGURE 2. Distribution of patients according to the most severe or complex type of ventricular arrhythmia during hypokalemia and after plasma potassium (K^+) correction. Changes are not statistically significant. PVCs = premature ventricular contractions.

hypokalemia, and of those, 1 patient had runs of ventricular tachycardia. Only these 7 patients received spironolactone for hypokalemia correction and they showed an improvement in ventricular ectopic activity after plasma potassium was restored. Again, selecting only the patients with increased ventricular ectopic activity for potassium repletion favors the possibility of improvement of ventricular ectopic activity by chance and diminishes the possibility of worsening of ventricular ectopic activity. It is not known what might have happened to the 14 patients who had minimal ventricular ectopic activity during hypokalemia had they received potassium-correcting therapy. By chance, their ventricular ectopy might have increased after plasma potassium correction, blunting the results of the group as a whole. Finally, in Holland's study hydrochlorothiazide was either decreased or discontinued in all 7 patients who received spironolactone for potassium repletion. Therefore, it is difficult to correlate changes in ventricular ectopic activity with plasma potassium concentrations because there was not only a changed plasma potassium level, but also, at the same time, a reduction or elimination of hydrochlorothiazide.

In our study, patients were selected by only 2 criteria: evidence of diuretic-induced hypokalemia and freedom from known heart disease. All medication, including the diuretic, remained unchanged throughout the study. Antihypertensive therapy was maintained, because some of our patients had severe hypertension that required up to 3 drugs to be controlled. It is unlikely that continuation of antihypertensive agents prevented any cardiac arrhythmias from appearing. In both the study of Holland et al and our study, approximately one third of the patients presented with more than minimal ventricular ectopic activity during the hypokalemic phase. In this study, all patients had treatment to correct plasma potassium, and 3 patients (Patients 1, 7 and 14) with minimal ventricular ectopic activity during hypokalemia developed couplets after plasma potassium correction. Although this may have been due to chance, obviously it adversely affects the average response of the entire group to potassium repletion.

The issue of the arrhythmogenic potential of hypokalemia was addressed in a recent editorial by Harrington et al,[16] who reviewed the literature and concluded that the published experience discloses no evidence that fatal ventricular ectopic activity results from hypokalemia per se. Others,[17] in agreement with our study, found no change in ventricular ectopic activity in hypertensive patients without known heart disease, during hypokalemia or after hypokalemia correction compared with the prediuretic period.

Recent reports implicate magnesium depletion as a cause of cardiac arrhythmias. Dyckner and Wester[18–20] studied ventricular arrhythmias in a group of hypokalemic patients with congestive heart failure, hypertension or liver disease. They observed no significant change in the frequency or type of ventricular arrhythmias after correction of serum potassium. Intracellular potassium also remained unchanged, whereas serum potassium increased from 3.40 to 4.27 mEq/liter.[18] In contrast, magnesium infusion led to an increase in cellular potassium content and a concomitant decrease in the frequency of PVCs.[20] In the present study it seems unlikely that magnesium played an important role in the persistence of cardiac arrhythmias before and after plasma potassium correction. Plasma magnesium was within the normal range (1.3 to 2.1 mEq/liter) averaging 1.49 ± 0.06 mEq/liter before and 1.59 ± 0.06 mEq/liter after correction of hypokalemia and did not correlate with cardiac arrhythmias. Although unlikely, the possibility of having intracellular magnesium depletion despite normal plasma values cannot be ruled out. Other investigators[21] believe that magnesium can only induce experimental arrhythmias at concentrations that are unphysiologic and even incompatible with life.

Why cardiac arrhythmias should persist after correction of hypokalemia is not clear. We suggest 2 hypotheses. The first is that the arrhythmias observed in this study may have had no relation to potassium deficit or hypokalemia. If so, correction of plasma potassium levels would not decrease the incidence of such arrhythmias. Ventricular arrhythmias may occur in patients without cardiovascular disease. Brodsky et al[22] found that 50% of 50 male medical students without cardiovascular disease and with normal echocardiograms had PVCs on ambulatory electrocardiographic

recordings, but only 1 had more than 50 in 24 hours. One medical student had ventricular couplets and 1 had a short episode of ventricular tachycardia. Clarke et al[23] performed 2 consecutive 24-hour recordings in 86 subjects, aged 16 to 65 years, who had no clinical evidence of cardiovascular disease. Ventricular ectopic beats were seen in 63 subjects, 7 of whom averaged more than 5 per hour. Thirteen subjects had multiform ventricular ectopic beats, 3 bigeminy, 2 R-on-T phenomenon and 2 brief episodes of ventricular tachycardia. Arrhythmias were more frequent in the older patients. In our patients also, older patients tended to have more cardiac arrhythmias during both monitorings (Tables I and III).

The second hypothesis is that the arrhythmias indeed were related to potassium depletion, but they failed to respond to the correction of plasma potassium levels because there was no concomitant change in intracellular potassium. Although electrophysiologic events on the myocardial cell are influenced by cations like calcium, sodium or magnesium, under clinical conditions, the resting membrane potential is determined primarily by the concentration gradient for potassium across the membrane.[24] Changes in the ratio between intracellular and extracellular potassium will have an impact on the resting membrane potential, according to the formula[18,20]: resting membrane potential = −61.5 log intracellular potassium/extracellular potassium. A relative decrease in intracellular potassium or an increase in extracellular potassium leads to a less negative resting membrane potential; the cell approaches the threshold of excitation and the conduction is slowed in the ventricle, promoting reentrant circuits.[18,20,21]

Whether diuretic therapy results in depletion of total body potassium stores is controversial,[4,25–27] but several investigators have shown that there is no increase in intracellular potassium with potassium supplements in patients treated with a diuretic.[25,28,29]

The moderate, but not significant, shift of our patients toward more complex arrhythmias and the increase in the number of patients with couplets after correction of plasma potassium are not necessarily associated with correction of hypokalemia because this shift can be attributed to the spontaneous variation that may occur in consecutive 24-hour ambulatory electrocardiographic monitorings.[14,15]

Acknowledgment: We are indebted to Barbara Lynn Davis, CVT, and to Aldo Notargiacomo, BS, for excellent technical assistance.

References

1. Veterans Administration Cooperative Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension. III. Influence of age, diastolic pressure, and prior cardiovascular disease; further analysis of side effects. Circulation 1972;45:991–1004.
2. **Gifford RW, Jr.** Combined drug therapy of hypertension. In: Hahnemann Symposium on Hypertensive Disease (1958). Hypertension. Pennsylvania: WB Saunders, 1959:361.
3. **Kassirer PJ, Harrington TJ.** Diuretics and potassium metabolism: a reassessment of need, effectiveness and safety of potassium therapy. Kidney Internat 1977;11:505–515.
4. **Wilkinson RP, Hesp R, Issler H, Raftery BE.** Total body potassium during prolonged thiazide therapy for essential hypertension. Lancet 1975;1: 759:62.
5. **Lawson HD.** Adverse reaction to potassium chloride. Quart J Med 1974; 171:433–440.
6. **Lown B, Levine HD.** Atrial arrhythmias, Digitalis and Potassium. New York: Lansberger, 1958.
7. **Fisch C, Surawicz B.** Digitalis. New York: Grune & Stratton, 1969.
8. **Pick A.** Arrhythmias and potassium in man. Am Heart J 1966;72:295–306.
9. **Davidson S, Surawicz B, Ky L.** Ectopic beats and atrioventricular conduction disturbances in patients with hypopotassemia. Arch Intern Med 1967; 120:280–285.
10. **Harrison DC, Fitzgerald JW, Winkle RA.** Contribution of ambulatory electrocardiographic monitoring to antiarrhythmic management. Am J Cardiol 1978;41:996–1004.
11. **Lown B.** Sudden cardiac death: the major challenge confronting contemporary cardiology. Am J Cardiol 1979;43:313–328.
12. **Colton T.** Statistics in Medicine. Boston: Little Brown, 1974:149–165.
13. **Holland OB, Nixon JV, Kuhnert I.** Diuretic-induced ventricular ectopic activity. Am J Med 1981;70:762–768.
14. **Morganroth J, Michelson EL, Horowitz LN, Josephson ME, Pearlman AS, Dunkman WB.** Limitations of routine long-term electrocardiographic monitoring to assess ventricular ectopic frequency. Circulation 1978;58: 408–414.
15. **Michelson EL, Morganroth J.** Spontaneous variability of complex ventricular arrhythmias detected by long-term electrocardiographic recording. Circulation 1980;61:690–695.
16. **Harrington JT, Isner JM, Kassirer JP.** Our national obsession with potassium. Am J Med 1982;73:155–159.
17. **Caralis P, Perez-Stable E, Materson B, Rozansk J.** Ventricular ectopy and diuretic-induced hypokalemia in hypertensive patients (abstr). Clin Res 1981;29:832A.
18. **Dyckner T, Wester PO.** Ventricular extrasystoles and intracellular electrolytes in hypokalemic patients before and after correction of the hypokalemia. Acta Med Scand 1973;204:357–359.
19. **Dyckner T, Wester PO.** Intracellular potassium after magnesium infusion. Br Med J 1978;1:822–823.
20. **Dyckner T, Wester PO.** Ventricular extrasystoles and intracellular electrolytes before and after potassium and magnesium infusion in patients on diuretic treatment. Am Heart J 1979;97:12–18.
21. **Fisch C.** Relation of electrolyte disturbances to cardiac arrhythmias. Circulation 1973;47:408–419.
22. **Brodsky M, Wu D, Denes P, Kanakis C, Rosen K.** Arrhythmias documented by 24-hour continuous electrocardiographic monitoring in 50 male medical students without apparent heart disease. Am J Cardiol 1977;39:390–395.
23. **Clarke JM, Hamer J, Shelton JR, Taylor S, Venning GR.** The rhythm of normal human heart. Lancet 1976;2:508–512.
24. **Anderson KE.** The heart cell: electrophysiological aspects. Acta Med Scand 1981;647:7–13.
25. **Leemhuis MP, VanDamme KJ, Strayvenberg A.** Effects of chlorthalidone on serum and total body potassium in hypertensive patients. Acta Med Scand 1976;200:37–45.
26. **Hersp R, Wilkinson PR.** Potassium supplementation of thiazide therapy (letter). Lancet 1976;2:1144.
27. **Edmonds CS, Jasani B.** Total body potassium in hypertensive patients during prolonged diuretic therapy. Lancet 1972;2:8–12.
28. **Down PF, Polak A, Rao R, Mead JA.** Fate of potassium supplements in six outpatients receiving long-term diuretics for oedematous disease. Lancet 1972;2:721–724.
29. **Dargie HJ, Boddy K, Kennedy AC, King PC, Read PR, Ward DM.** Total body potassium in long-term frusemide therapy: is potassium supplementation necessary? Br Med J 1974;4:316–319.